IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)
Daisuke TENMIZU et al.	) Group Art Unit: 1634
Application No.: 10/536,809	) Examiner: Jeanine Anne GOLDBERG
371(c) Date: May 27, 2005	)
International Filing Date: May 28, 2004	) Confirmation No.: 4582
For: CANINE CYP1A2 GENETIC POLYMORPHISM	)

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Commissioner for Patents
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Sir:

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(i)

Please make of record in the file of this case the documents listed on the attached IDS Form PTO/SB/08, copies of which are enclosed.

Applicants provide the following as concise statements of relevance of the non-English language documents.

1. KATO and KAMATAKI, ed., "YAKUBUTSUTAISHAGAKU: IRYOUYAKUGAKU -- DOKUSEIGAKU NO KISO TOSHITE", 2d. ed., TOKYO KAGAKU DOUJIN, Oct. 2000, p.9-19, relates to the following description on page 1, line 17 to page 2, line 18 of the present specification.

> "Drug metabolism is a change in a chemical structure of a compound caused by an enzymatic action in a living body. Such an enzym [sic], contributing to drug

metabolism, is called a drug metabolizing enzyme. Drug metabolizing enzymes are considered originally to catalyze synthetic reactions or decomposition reactions of biomolecules such as steroids, fatty acids, or bile acids, but can metabolize drugs administered to or invading the body (i.e., foreign substances), whereby the foreign substances are eliminated from the body.

A drug metabolizing reaction is basically composed of a phase I reaction and a phase II reaction. In the phase I reaction, one or more polar functional groups are introduced to a drug by oxidation, reduction, and/or hydrolysis. In the phase II reaction, one or more biomolecules such as glucuronic acid, sulfuric acid, or glutathione are bound to the functional group(s) generated in the phase I reaction. The phase I and phase II reactions impart an excellent water-solubility to the drug, and as a result, the drug is easily excreted from the body.

[0003]

Metabolizing enzymes contributing to approximately 80% of all phase I drug metabolizing reactions are called "cytochrome P450" (hereinafter referred to as "CYP"). CYPs have a molecular weight of approximately 50000 and contain a protoheme as a prosthetic group. When an average molecular weight of an amino acid is regarded as 100, CYP is composed of approximately 500 amino acids. In the classification and nomenclature of CYPs, CYPs are systematically denoted by placing an Arabic numeral indicating a "family" and an alphabetic character indicating a "subfamily" after "CYP". A group of CYP molecules showing a homology (amino acid sequence) of more than 40% is regarded as a family. A group of CYP molecules showing a homology of more than 55% is regarded as a subfamily. When a family contains two or more subfamilies, the subfamilies are denoted in alphabetical order (for example, CYP2A, CYP2B, and CYP2C). Plural CYP molecules contained in a subfamily are denoted by placing an additional Arabic numeral suffix (for example, CYP1A1). At present, Families 1 to 4 are known as drug-metabolism-type CYPs in mammals (non-patent reference 1)."

2. KATO and KAMATAKI, ed., "YAKUBUTSUTAISHAGAKU: IRYOUYAKUGAKU -- DOKUSEIGAKU NO KISO TOSHITE", 2d. ed., TOKYO KAGAKU DOUJIN, Oct. 2000, p.19-20, relates to the following description on page 3, lines 6-17 of the present specification.

> "A human CYP1 family includes two subfamilies A and B, which are induced by polycyclic aromatic hydrocarbons (such as 3-methylcholanthrene) or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin). The drug metabolizing mechanism in the CYP1 family is best maintained among CYPs, and thus substrate specificity in humans is very similar to that of laboratory animals. Oxidation of carcinogenic polycyclic aromatic hydrocarbons or mycotoxins, or hydroxylation of nitrogen atom(s) in aromatic amines or heterocyclic amines are typical reactions, and the CYP1 family is closely associated with a metabolic activation of a carcinogen (non-patent reference 10)."

3. KATO and KAMATAKI, ed., "YAKUBUTSUTAISHAGAKU: IRYOUYAKUGAKU -- DOKUSEIGAKU NO KISO TOSHITE", 2d. ed., TOKYO KAGAKU DOUJIN, Oct. 2000, p.141-155, relates to the following description on page 4, lines 21-35 of the present specification.

> "Thiopurine S-methyltransferase (hereinafter referred to as TPMT) is an enzyme which catalyzes methylation of some thiopurine drugs. TPMT is mainly located in the liver, but also is located in erythrocytes, and thus erythrocytes are used to analyze phenotypes in humans. When a TPMT activity in erythrocytes is used as an index, activities in whites exhibited a triphasic profile. A group exhibiting a high activity accounted for 88.6%, a group exhibiting a middle activity accounted for 11.1%, and a group exhibiting a low activity accounted for 0.3%. Evans et al. analyzed a TMPT gene in a leukemia patient with acute pancytopenia by 6-mercaptopurine, and

revealed that the gene had three point mutations (TPMT*2, TPMT*3A, and TPMT*3C) with amino acid substitutions which caused the disappearance of the enzyme activity (non-patent reference 16)."

4. OTOKAWA, "INO NO SEIBUTSUGAKU" 1st ed., ASAKURA SHOTEN, Sept. 1969, p. 179-187, relates to the following description on page 2, lines 24-25 of the present specification.

"The most preferable variety meeting the above conditions is a beagle (non-patent reference 2)."

An English language version of Bertilsson, 2002, non-patent reference 12, that appeared in Pharmacogenomics, KALOW et al. (eds.), Vol. 113, p. 33-50, is enclosed. An English translation of MIYASHITA et al. 2002, Poster 20PE-46 from the 17th Annual Meeting of the Japanese Society for the Study of Xenobiotics, non-patent reference 21, is also enclosed.

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." If the Examiner applies any of the documents as prior art against any claim in the application and Applicants determine that the cited documents do not constitute "prior art" under United States law, Applicants reserve the right to present to the Office the relevant facts and law regarding the appropriate status of such documents.

Applicants further reserve the right to take appropriate action to establish the patentability of the claimed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

If there is any fee due in connection with the filing of this Statement, please charge the fee to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: November 12, 2007

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